### REMARKS

In the Office Action of December 12, 1997, the Examiner has rejected claims 2, 5, 6, 8, and 10-12, objected to claims 7 and 9 and withdrawn claim 1, 3, and 4 from consideration. In this amendment, applicants amend claim 5 and add claim 13. As such claims 1-13 are pending for examination. Support for the amendment to claim 5 is found, for example, on pages 12-15 which discuss recombinant production of human PAP and pages 15-17 which discuss dephosphorylation of a substate. Support for claim 13 is found in orginally filed claim 10.

### I. Election With Traverse

Applicants acknowledge that during a telephone conversation on October 30, 1997, applicants' representative elected claims 2 and 5-12 with traverse. Applicants' reason for traverse is that it would not present an undue burden for the Examiner to consider the non-elected claims along with the elected claims.

## II. §102 Rejection Over Boder et al.

The Examiner has rejected claims 5, 10, and 11 as anticipated by Boder et al., Cellular Signalling 6:933-41 (1994). Claim 5, as amended, recites a step of "recombinantly producing a human phosphatidic acid phosphatase protein." This step is neither taught or suggested by the Boder reference. Accordingly, applicants respectfully request that the Examiner withdraw the rejection of claims 5, 10, and 11 over the Boder reference. Furthermore, applicants maintain that added claim 13 is not anticipated by Boder et al. because, inter alia, Boder does not disclose the substrates recited in claim 13.

# III. §103 Rejection Over Kai et al. In View of Genbank Entries AA040858, W04968, and H68363

The Examiner has rejected claims 2, 5, 6, and 10-12 as obvious over Kai et al., J. Biol. Chem. 271:18931-38 (1996) in view of Genbank Entries AA040858, W04968, and H68363. Applicants respectfully traverse.

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## A. Claims 5 and 10-12

Applicants maintain that the cited Genbank entries do not render obvious claims 5 and 10-12. Applicants note that the Genbank entries are Expressed Sequence Tags (ESTs), and in particular, the cited entries are cDNA sequence fragments that have been randomly sequenced from the 3' (the polyadenylation tail) end of a transcript derived from a human cDNA library of various tissues. The Genbank entries describe no putative start codon, stop codon or function to the perspective sequences. such, the cited ESTs would not have lead the skilled artisan to believe that the cited fragments encoded any particular protein. In fact, it is often the case that ESTs do not contain any coding sequences but only list regulatory sequences. Accordingly, applicants believe that the cited ESTs fail to teach or suggest claimed human phosphatidic acid phosphatase protein (hereinafter "human PAP protein").

Furthermore, applicants respectfully traverse the Examiner's assertion that the cited homology between the Genbank entries and the murine and porcine sequences of the Kai reference would have rendered obvious the subject matter of claims 5 and 10-12. Specifically, the Examiner has stated that "it would have been obvious to one of ordinary skill in the art [based on the cited homology] that there is a human homolog of the PAP of Kai et al. which is highly homologous to the mouse and porcine proteins." Applicants respectfully disagree and submit that the existence of a cDNA fragment with homology to the Kai sequence would not have indicated the existence of a full length functional human PAP protein.

# B. Claims 2 and 6

Applicants traverse the Examiner's rejection of claims 2 and 6 for the same reasons given above. Moreover, applicants believe claims 2 and 6 are further patentable for the following reasons. Applicants submit that the Federal Circuit has emphasized the importance of structural obviousness in establishing a case of *prima facie* obviousness of DNAs and amino

acids. In particular, in *In re Deuel*, 51 F.3d 1552, 1558, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995) the court noted "Normally, a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound." In particular, the court held that the prior art teaching of a 19 amino acid N-terminal sequence did not render obvious claims to particular DNAs because "one could not have conceived the subject matter of claims 5 and 7 based on the teachings in the cited prior art because, until the claimed molecules were actually isolated and purified, it would have been highly unlikely for one of ordinary skill in the art to contemplate what was ultimately obtained. What cannot be contemplated or conceived cannot be obvious." Id. (emphasis added).

Applicants maintain that the holding of *In re Deuel* governs in the instant situation. That is, the cited fragment cannot render obvious claims directed to specific full-length amino acid sequences because the skilled artisan could not have contemplated the remaining amino acids. As stated by the court, "[w] hat cannot be contemplated or conceived cannot be obvious." Moreover, applicants submit that the teachings of the Kai reference do not remedy this defect in the cited Genbank entries.

# III. §103 Rejection Over Kai $et\ al$ . In View of Genbank Entry U79294

The Examiner has rejected claims 5, 8 and 10-12 as obvious over the Kai reference in view of Genbank Entry U79294. The Examiner maintains that "In view of the sequence identity between the cDNA of GENBANK entry U79294 and the mouse PAP cDNA of Kai et al., it would have been obvious to one of ordinary skill in the art that the cDNA disclosed by GENBANK entry U79294 encodes a human PAP." Specifically, the Examiner states that the cDNA of the cited entry "is identical to bases 225-1362 of SEQ ID NO:6 [sic; SEQ ID NO:5] (except for a single base deletion which is virtually certainly a sequencing error and not an actual difference in the nucleotide sequence) encompassing all of the

coding sequence of SEQ ID NO:5. This cDNA also exhibits 62% sequence identity with the mouse cDNA encoding PAP of Kai et al."

# A. Claims 5, and 10-12

With regard to claims 5 and 10-12, applicants submit that the cited Genbank entry does not suggest a human PAP protein, but in fact teaches away from such a protein. Applicants submit that the cited Genbank entry discloses a nucleic acid sequence encoding a putative protein having a stop codon at position 234. (Applicants include herein as ATTACHMENT A an amino acid comparison of the cited Genbank entry and the amino acid sequence encoded by SEQ ID NO:5 as well as a nucleic acid sequence comparison; the Examiner will note that the putative sequence of the cited Genbank entry contains a stop codon (\*) at amino acid position 234.)

submit that the skilled Applicants artisan knowledge of applicants' disclosed sequence would have assumed the fidelity of the cited Genbank entry. As such, the skilled artisan would have believed that the protein encoded by Genbank reference was 234 amino acids in length based on the stop codon at this position. Accordingly, applicants submit that the skilled artisan, being unaware of the sequences discovered by the instant inventors would not have concluded, as did the Examiner, that the stop codon at position 234 results from "virtually certainly a sequencing error."

In this vein, applicants submit that the putative 234 amino acid sequence of the cited Genbank entry when compared to the considerably longer deduced 283 amino acid sequence disclosed by the Kai reference would have lead the skilled artisan to believe that the cited Genbank entry did not encode human PAP. Applicants see no reason, and the Examiner has provided no reason, why the skilled artisan would have disregarded the actual sequence disclosed in the Genbank entry and the existence of a stop codon at position 234.

Applicants submit that a 62% homology standing alone would not lead a skilled artisan to believe that the cited Genbank

entry represented a homologue of the sequence disclosed by the Kai reference. Specifically, whether a specific percentage of sequence identity would lead the skilled artisan to believe that an unidentified sequence represents a homologue of a known sequence depends on an examination of the specific regions of homology and a determination of whether these regions are believed to represent conserved sequences that would indicate a species homologue. The Examiner, however, has provided no teaching in the art that the regions representing the 62% identity would have led the skilled artisan to believe that the cited Genbank sequence is a human homologue of the murine sequence disclosed by the Kai reference.

Moreover, even if the art would have led the skilled artisan to believe that the Genbank sequence might be a homologue to the Kai murine sequence, in the eyes of the law this would have only represented, at most, an invitation to experiment, which is insufficient support for an obviousness rejection. Applicants submit that a prima facie showing of obviousness requires a showing of likelihood of success, and applicants submit that the Examiner's citation of a 62% identity does not satisfy this requirement. Specifically, applicants point out that it was not known at the time of the filing of this application the degree of homology that a human PAP protein would exhibit when compared to the murine variety of the enzyme.

In fact, applicants submit that the lack of predictability inherent in using the disclosed murine sequence to gauge the existence of a human homologue is evidenced by the fact that the Kai reference disclosed a single PAP protein. In contrast, the present inventors have found that human PAP exists in at least four isoforms, denominated by the inventors as PAP- $\alpha$ (1 and 2), PAP- $\beta$  and PAP- $\gamma$ .

Given the teaching of the Kai reference, the skilled artisan would have believed that human PAP existed as a single isoform, when in fact, there are at least four different isoforms of PAP which are expressed by humans. Applicants believe that this discrepancy evidences that a homology of 62% between the

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cited Genbank entry and the Kai murine sequence would not have suggested with a reasonable likelihood of success that the cited Genbank entry encodes a human PAP protein that could be used for dephosphorylating a substrate.

#### В. Claim 8

With regard to claim 8, applicants submit that this claim is further patentable because the cited references do not teach the specific amino acids claimed for the reasons mentioned above.

#### v. Conclusion

In view of the above remarks and amendments, applicants believe this application to be in condition for allowance and such a Notice is respectfully requested.

Respectfully submitted,

March 3, 1990

Reg. No. 41,104

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> Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby motition for any model extension of time hereby petition for any needed extension of time.

# Comparison of Genbank U79294 to Cti human PAP- $\beta$

		10	20	30	40	50
U79294.AMI	1	MONAKARKYT	<b>VPESIONGGSP</b>	ALNNUFEESG	SERVILLICAL	LTCLFNAGLE
PAP B.AMI	1	MONYKYDKAL	VPESINGGSP	ALBINDPERSO	SERVELLICED	DYCLENAGED
<del>-</del> /		60	70	80	90	100
U79294.AMI	51	FLITETTIK	PZHKGEYCND	ES IKYPLETG	ELIMBERLEA	VCTVIAITAI
PAP_B.AMI	51	FLATETSTIK	FZHRHFYCNO	ENTHYPLETO	ETINDAVLLA	VAIVISITAT
		110	120	130	140	150
U79294.AMI	101	1.000 / 2.000	TAKERSTION	CYVAAD/KOV	<b>GCFTPGBALS</b>	CHPTLIANCE
PAP_B.AMI	101	TIGEP 2ALIYY	TRESTLON	PTVAALUKUV	<b>GCFLFGEAIS</b>	CONTINUARY
		160	170	180	190	200
U79294.AMI	151	<b>ECREPHIELS</b>	VCMPDESQIN	CSECVIONYR	CRGDDSKVQB	ARICE EE SGID.
PAP_B.AMI	151	TORGET PAPES	VCNPPESCIN	CSEGVICIVA	CRGCCSKVCB	ARKS FEBRUAR
		210	220	230	240	250
U79294.AMI	201	Sesmytmiyi	VLYLCARFIN	RCARCSGRSC	SSP*	
PAP_B.AMI	201	SESMYTMLYL	VIVIOAREIW	REALLRELL	QFTLIMMAFY	TGLSRVSDHK
		260	270	280	290	300
U79294.AMI	251					
PAP_B.AMI	251	HHPSDVLAGF	AQGALVACCI	VFFVSDLFKT	KTTLSLPAPA	IRKEILSPVD
		310	320	330	340	350
U79294.AMI	301					
PAP_B.AMI	301	IIDRNNHHNM	M*			· · · · · · · · · · ·

Comparison of full DNA sequence of Genbank U79294 and Cti human PAP- $\beta$ 

U79294.TXT	80 GGCCGAGCGC	90 CCGCGCTGC				130 CGCCACAACAGC
PAP_B.DNA	GGCGCAGCTC		TTCTGCTCG			: :: :: TG-GACTTTAGA 50
U79294.TXT	140	150 CTGCGCAGO	160 TCTGCAAAA	170 GTTTCTGCTC	180 GGGATCTGGC	190 PCTCTTCCCCTT
PAP_B.DNA		: ::: GTTGACAG- 0	-AGGAAAGC	AGAGGCGCGC 90	AGGA-GGAGC	: :: AGAAAACACCAC 110
U79294.TXT					240 AGGCG-CGCA :: :: :::	250 GGAGGAGCAGAA ::::::
PAP_B.DNA	120	TGGAGGCAG	GCAGCCCCG 140	GCTGCACTCT 150	AGCCGCCGCG	CCCGGAGCCG 170
U79294.TXT	: :::	: : :	: ::::	: : X: ::	:: :	310 GCCGCCTGGGTG
PAP_B.DNA	GGGCCGACCC 180 320	GCCACTATO 190 330	200	210	220	GGCGCCTGGGTG 230
U79294.TXT	TGTGGCTGCT	GTTGCGGGA				370 CAGCCAGCGCCA
PAP_B.DNA	240	250	260	270	280	CAGCCAGCGCCA 290
U79294.TXT			CAAAGCGAT			430 GCGGCAGCCCGG
PAP_B.DNA	TGCAAAACTA 300 440	CAAGTACGA 310 450	ACAAAGCGAT 320 460	CGTCCCGGAG 330 470	AGCAAGAACG 340	GCGGCAGCCCGG 350
U79294.TXT	CGCTCAACAA	CAACCCGAG	GAGGAGCGG	CAGCAAGCGG	::::::::	490 rctgcctcgacc
PAP_B.DNA	CGCTCAACAA 360 500	CAACCCGAG 370 510	GAGGAGCGG 380 520	CAGCAAGCGG 390 530	GTGCTGCTCA' 400 540	CTGCCTCGACC 410 550
U79294.TXT	TCTTCTGCCT	CTTCATGGC	GGGCCTCCC	CTTCCTCATC	ATCGAGACAA	GCACCATCAAGC
PAP_B.DNA	TCTTCTGCCT 420 560	CTTCATGGC 430 570	GGGCCTCCC 440 580	CTTCCTCATC 450 590	ATCGAGACAA 460 600	GCACCATCAAGC 470 610
U79294.TXT	CTTACCACCG	AGGGTTTTA	ACTGCAATGA	TGAGAGCATC	AAGTACCCAC	TGAAAACTGGTG
PAP_B.DNA	480 620	AGGGTTTTA 490 630	ACTGCAATGA 500 640	TGAGAGCATC 510 650	AAGTACCCAC 520 660	FGAAAACTGGTG 530 670
U79294.TXT	AGACAATAAA	TGACGCTG1	GCTCTGTGC	CGTGGGGATC	GTCATTGCCA'	CCTCGCGATCA
PAP_B.DNA	AGACAATAAA 540 680	TGACGCTGT 550 690	GCTCTGTGC 560 700	CGTGGGGATC 570 710	GTCATTGCCA: 580 720	ICCTCGCGATCA 590 730
U79294.TXT	TCACGGGGGA	ATTCTACCO	GATCTATTA	CCTGAAGAAG :::::::::::	TCGCGGTCGA	CGATTCAGAACC
PAP_B.DNA	600 740	610 750	620 760	630 770	76GCGGTCGA0 780	CGATTCAGAACC 650 790
U79294.TXT	:::::::::	:::::::		::::::::	CTCTTTGGCT	
PAP_B.DNA	660 800	670 810	680 820	690 830	700 840	GTGCCATCAGCC 710 850

U79294.TXT	AGTCTTTCACAC	GACATTGCCAA	AGTGTCCATA	AGGGCGCCTGC	GTCCTCACTI	CTTGAGTG
	:::::::::::	:::::::::	:::::::::::::::::::::::::::::::::::::::	:::::::::::::		
PAP_B.DNA	AGTCTTTCACAC					
	720	730	740	750	760	770 910
	860	870	880	890	900 ***********************************	
U79294.TXT	TCTGCAACCCT					
	TCTGCAACCCTC			::::::::: :mcmcx		 \CTACAGAT
PAP_B.DNA		790	800	810	820	830
	780 920	930	940	950	960	970
U79294.TXT	GCAGAGGTGAT					
0/9294.IXI	:::::::::::		·····	······		
מומים מוגמ	GCAGAGGTGAT		CCACCAACC	TAGGAAGTCCT	יייכיייכייכייכי	CCATGCCT
PAP_B.DNA	840	850	860	870	880	890
	980					1030
U79294.TXT	CCTTCTCCATG					
0/9294.181	:::::::::::					
PAP B.DNA	CCTTCTCCATG		CTATTTGGT	CTATACCTGO	AGGCCCGCT	CACTTGGC
FAF_B.DMA	900	910	920		940	950
	1040	1050	1060	1070	1080	1090
U79294.TXT	GAGGAGCCCG					
0/3234.171	::::::::				:::::::::::::	: : : : : : : :
PAP_B.DNA	GAGGAGCCCG		· CCTCCTGC A	TTTC ACCTTG	ATCATGATGG	CCTTCTACA
FAF_B.DNA	960	970	980	990	1000	1010
	1100	1110	1120	1130	1140	1150
U79294.TXT	CGGGACTGTCT					
0/9294.171	:::::::::					
PAP B.DNA	CGGGACTGTCT	CCCCTATCAC	CCACAAGCA	CCATCCCAGT	GATGTTCTGG	CAGGATTTG
FAF_D.DNA	f 1020	1030	1040	1050	1060	1070
	1160	1170	1180	1190	1200	1210
U79294.TXT	CTCAAGGAGCC					
0,3237.17.1	::::::::::					
PAP B.DNA	CTCAAGGAGCC					
	1080	1090	1100	1110	1120	1130
	1220	1230	1240	1250	1260	1270
U79294.TXT	AGACGACGCTC				ATCCTTTCAC	CTGTGGACA
0.525	::::::::::	:::::::::	: : : : : : : : :	:::::::::	::::::::	::::::::
PAP B.DNA	AGACGACGCTC	TCCCTGCCTG	CCCTGCTAT	CCGGAAGGAA	ATCCTTTCAC	CTGTGGACA
	1140	1150	1160	1170	1180	1190
	1280	1290	1300	1310	1320	1330
U79294.TXT	TTATTGACAGG.				CCCACCTCCT	GAGCTGTTT
0.727.71	:::::::::::					
PAP B.DNA	TTATTGACAGG.	AACAATCACC	ACAACATGAT	GTAGGTGCCA	CCCACCTCCT	GAGCTGTTT
····· _5······	1200	1210	1220	1230	1240	1250
	1340	1350	1360	1370	1380	1390
U79294.TXT	TTGTAAAATGA	CTGCTGACAG		CTGCTCTCCA	ATCTCATCAG	ACAGTAGAA
	::::::::::					
PAP_B.DNA	TTGTAAAATGA	CTGCTGACAG	CAAGTTCTTG	CTGCTCTCCA	ATCTCATCAG	ACAGTAGAA
	1260	1270	1280	1290	1300	1310 .
	1400	1410	1420	1430	1440	
U79294.TXT	TGTAGGGAAAA					
	::::::::::					
PAP B.DNA	TGTAGGGAAAA					
<u>-</u>	1320	1330.	1340	1350	1360	
	-					

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